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Published in:
European Journal of Surgical Oncology

DOI:
[10.1016/j.ejso.2006.10.035](https://doi.org/10.1016/j.ejso.2006.10.035)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2007

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Grossmann, I., de Bock, G. H., Kranenbarg, W. M. M-K., de Velde, C. J. H. V., & Wiggers, T. (2007). Carcinoembryonic antigen (CEA) measurement during follow-up for rectal carcinoma is useful even if normal levels exist before surgery. A retrospective study of CEA values in the TME trial. *European Journal of Surgical Oncology*, 33(2), 183-187. <https://doi.org/10.1016/j.ejso.2006.10.035>

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Carcinoembryonic antigen (CEA) measurement during follow-up for rectal carcinoma is useful even if normal levels exist before surgery. A retrospective study of CEA values in the TME trial

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Accepted 24 October 2006

Available online 15 December 2006

Abstract

Background: Carcinoembryonic antigen (CEA) as a marker in the follow-up after curative resection of colorectal carcinoma (CRC) is often omitted from follow-up despite guideline recommendations. One reason is the assumption that when a normal CEA value exists before curative resection of CRC, it will neither rise during follow-up. This study investigates this relationship.

Method: Data were derived from a study initiated to evaluate treatment regimes for rectal carcinoma (Dutch TME trial, $n = 1861$) from which 954 were eligible for analysis. Recurrent disease occurred in 272 of these patients (29.5%). The pre-operative CEA value was compared to CEA values during follow-up, using threshold values of 2.5 and 5.0 ng/ml.

Results: Normal pre-operative CEA values were present in 63% ($CEA < 5.0$) and 39% ($CEA < 2.5$) of patients with recurrent disease. Patients with a normal pre-operative CEA and recurrent disease had elevated CEA values during follow-up in 41% ($CEA < 5.0$), 50% ($CEA < 2.5$) and in 60% with both threshold values when the last measurement was done within 3 months before recurrent disease was diagnosed.

Conclusion: A normal pre-operative CEA is common in patients with rectal carcinoma. CEA does rise due to recurrent disease in at least 50% of patients with normal pre-operative values. Serial post-operative CEA testing cannot be discarded based on a normal pre-operative serum CEA.

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Keywords: Carcinoembryonic antigen; Colorectal neoplasm; Follow-up; Oncology

Introduction

Carcinoembryonic antigen (CEA) as a marker in the follow-up of colorectal carcinoma (CRC) has been subjected to debate concerning its effectiveness to reduce cancer mortality. CEA is known to have the ability to detect

recurrent disease after curative resection of CRC at an early stage, with approximately 5 months lead time compared to clinical signs and several other tests. The effect on survival is less clear, also due to the fact that only a minority of metastasis can be treated with curative intent. Several follow-up studies have been done with contradicting results, successively reflected in meta-analyses and reviews^{1–6} that conclude there is no consistent evidence that follow-up increases survival. The doubts about the value of CEA in follow-up contributes to decreasing adherence to guidelines from oncological societies,^{7–10} that generally advise to measure CEA every 3 months in the first 3 years.

Other arguments then lack of evidence may influence leaving CEA out of follow-up as well. One of these is the

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assumed relationship between serum CEA values before and after curative surgery for colorectal carcinoma. Normal pre-operative CEA values are often considered a reason to omit serum CEA measurements from follow-up, because it is widely believed it will not rise with recurrent disease either. This belief is expressed in one regional Dutch guideline advising ultrasound instead of CEA measurement when pre-operative levels are normal, and is also reported in a recent survey.¹¹

The threshold value of CEA is dependent on agreement; the industrial standard is 2.0–2.5 ng/ml dependent on the actual test. Due to frequent false-positive outcomes caused by benign gastro-intestinal disorders and smoking, the generally adhered threshold value in the follow-up for colorectal carcinoma in the Netherlands is 5.0 ng/ml.

In literature only little evidence is available about the relationship between CEA values before curative surgery and during follow-up. Staab et al.¹² were the first to describe the relationship between serum CEA values: he observed that in 40 patients with a normal pre-operative CEA value, none had risen during follow-up. Three other groups,^{13–15} however, published data that did demonstrate CEA elevations with recurrent disease when the serum CEA value before intended curative treatment was normal. The goal of this study is to evaluate the relationship between serum CEA values before and after curative resection of rectal carcinoma.

Patients and methods

Patients

An analysis was carried out on data derived from a study evaluating the value of short-course radiotherapy in primary resectable rectal carcinoma treated with standardized surgery (Total Mesorectal Excision or TME trial) from the Dutch ColoRectal Cancer group (DCRC-group). The results of this study were published previously.^{16,17} The registration included all actual CEA values that were measured. Serial CEA testing was required every 3 months in the first 3 years and every 6 months in year 4 and 5, according to the study protocol that was based on national guidelines. From January 1996 until December 1999, 1861 patients were included, and follow-up data are registered until March 2006; the minimal follow-up time is therefore more than 6 years. In this study, patients with stage 0 and IV were excluded. Of the remaining eligible patients, the pre-operative CEA value and at least one post-operative CEA value were required for inclusion in this analysis.

Methods

The definition of ‘pre-operative CEA’ is the serum CEA value measured immediately before curative resection of the primary tumour. ‘Post-operative CEA’ is the serum CEA value after primary surgery during follow-up. To

analyse the rise of CEA after curative resection in relationship to the pre-operative CEA value, we compared pre-operative values to the maximum post-operative value. This was done both for the group with and without recurrent disease. A separate analysis was performed for the group of patients with recurrent disease from whom the last post-operative CEA was determined less than 3 months before recurrent disease was diagnosed.

To analyse the response of CEA after curative surgery (expected decrease) we compared the pre-operative CEA to the minimum post-operative value in both the patients with and without recurrent disease. All analyses are retrospectively done using two different threshold values, being 2.5 ng/ml and 5.0 ng/ml. No statistical analysis was applicable.

Results

Studied cohort

After exclusion of stage 0 and IV patients, 1701 patients were eligible for analysis. Stage I–II–III rectal carcinoma was diagnosed in 1665 patients, 36 patients were not classified. Both pre- and post-operative CEA values were available in 954 patients (56%). From these 954 patients, recurrent disease was diagnosed in 282 patients (29.6%). Patient demographics and tumour characteristics are described in Table 1. The actual frequency of CEA measurements was much lower than required and was never above 50% at each moment (Fig. 1).

Relationship between pre- and post-operative CEA levels

In patients with recurrent disease ($n = 282$), 63% ($n = 179$) had a normal CEA value prior to primary surgery when apprehending a cut-off value of 5 ng/ml. Post-operative rise of the CEA above this threshold occurred in 41% ($n = 73$). When a cut-off value of 2.5 ng/ml was used, 39% ($n = 110$) had normal pre-operative CEA values. Elevated post-operative values were then found in 50% ($n = 55$) (Table 2). When the last CEA was measured within 3 months before diagnosis of local recurrence or metastasis ($n = 127$), CEA was elevated in 59% (with a threshold of 5 ng/ml) and 61% (with a threshold of 2.5 ng/ml) (Table 3).

In patients with no recurrent disease ($n = 672$), 77% ($n = 519$) had normal pre-operative CEA values when apprehending a cut-off value of 5 ng/ml. Post-operative rise of the CEA above this threshold during follow-up occurred in 4% ($n = 19$). When a cut-off value of 2.5 ng/ml was used, 50% ($n = 337$) had normal pre-operative CEA values. Elevated post-operative values were then found in 13% ($n = 44$).

In patients with recurrent disease ($n = 282$) and an elevated CEA value prior to primary surgery ($n = 172$ at a threshold of 2.5 ng/ml, $n = 103$ at a threshold of 5 ng/ml),

Table 1
Patient characteristics and tumour classification

	Eligible patients ^a (<i>n</i> = 1701)	Recurrent disease ^b (<i>n</i> = 282)	No recurrent disease ^b (<i>n</i> = 672)
Age (years) median (range)	66 (23–92)	64 (23–85)	64 (27–88)
Sex			
Male	63% (<i>n</i> = 1071)	67% (<i>n</i> = 189)	61% (<i>n</i> = 407)
Female	37% (<i>n</i> = 630)	33% (<i>n</i> = 93)	39% (<i>n</i> = 265)
Tumour classification ^c			
Stage I	30.5% (<i>n</i> = 519)	8.2% (<i>n</i> = 23)	39.9% (<i>n</i> = 268)
Stage II	29.9% (<i>n</i> = 508)	25.5% (<i>n</i> = 72)	31% (<i>n</i> = 208)
Stage III	37.5% (<i>n</i> = 638)	65.6% (<i>n</i> = 185)	28.3% (<i>n</i> = 190)
Unknown	2.1% (<i>n</i> = 36)	0.7% (<i>n</i> = 2)	0.9% (<i>n</i> = 6)

^a All patients that are eligible for inclusion in this analysis (all minus stage 0 and IV patients).

^b Eligible patients with known pre- and post-operative CEA values, in total 954 patients.

^c Tumour classification according to the American Joint Committee on Cancer (AJCC).

CEA values were also elevated during follow-up in 79% (*n* = 141 at a threshold of 2.5 ng/ml) and 82% (*n* = 81 at a threshold of 5 ng/ml) (Table 2).

CEA values were normal after curative surgery in 98% (*n* = 658 at a threshold of 5 ng/ml) and 86% (*n* = 578 at a threshold of 2.5 ng/ml) in all patients without recurrent disease (*n* = 672) during follow-up. When recurrent disease was diagnosed during follow-up (*n* = 282), CEA values were normal at the first measurement after curative surgery in 81% (*n* = 228 at a threshold of 5 ng/ml) and 66% (*n* = 186 at a threshold of 2.5 ng/ml).

Discussion

Summary of the results

This study suggests that a normal pre-operative CEA value does not mean it will not rise with, and due to

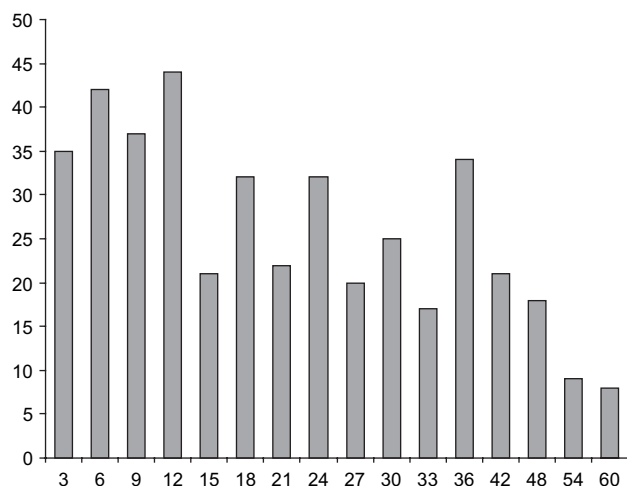


Figure 1. Actual measurement of CEA during follow-up in the TME trial. On the X-axis the moment in time CEA is recommended to be measured, in months after primary surgery. On the Y-axis the percentage (%) of actual measurements on that specific moment is given.

recurrent disease during follow-up. A non-elevated CEA at primary diagnosis is common (50%), as well as a rise in CEA despite a normal pre-operative CEA (50%); this situation thus applies to a quarter of all colorectal cancer patients.

Role of false-positive post-operative CEA levels influencing study results

Incidental rises in CEA due to benign disease or smoking are known and can be the cause of ‘falsely’ elevated CEA levels during follow-up. This may account for a part of the elevated post-operative CEA values in this study because a comparison was made of the pre-operative CEA value with the *maximum* CEA value during follow-up. The proportion of these falsely elevated CEA levels was estimated by performing the same analysis in patients with no recurrent disease. This turned out to be limited (4–13%). Further the pre-operative CEA was compared with the CEA value at the time of the diagnosis of recurrent disease, assuming at least these elevated CEA values are due to recurrent disease. The percentage in this group

Table 2
Relationship between CEA values before and after curative surgery^a in patients with recurrent disease (*n* = 282)

	Post-operative value < 2.5	Post-operative value > 2.5
Pre-operative value < 2.5	55	55 (50%) ^b
Pre-operative value > 2.5	31	141
	Post-operative value < 5.0	Post-operative value > 5.0
Pre-operative value < 5.0	106	73
Pre-operative value > 5.0	22	81

^a The pre-operative value was compared to the highest CEA value measured during follow-up.

^b The percentage of all patients with normal pre-operative CEA values (*n* = 110) with elevated post-operative values (*n* = 55)

Table 3
Relationship between CEA values before curative surgery and at diagnosis of recurrent disease^a ($n = 127$)

	Post-operative value < 2.5	Post-operative value > 2.5
Pre-operative value < 2.5	17	27 (61%) ^b
Pre-operative value > 2.5	7	76
	Post-operative value < 5.0	Post-operative value > 5.0
Pre-operative value < 5.0	28	40
Pre-operative value > 5.0	10	49

^a CEA value measured within 3 months before the diagnosis of recurrent disease was established.

^b The percentage of all patients with normal pre-operative CEA values ($n = 44$) with elevated post-operative values ($n = 27$).

was even higher (60%). The results of this study are in coherence with other numbers reported in literature.^{13–15}

Value of CEA immediately after primary surgery

Not all CEA values return to normal after curative surgery, especially in the group of patients that are diagnosed with recurrent disease during follow-up, due to residual microscopic disease at time of intended curative surgery. A persistent abnormal post-operative CEA usually indicates synchronous metastasis or irradical resection and is applicable as a marker for the effectiveness of curative surgery. Serum CEA has a half-life of 6–60 days, and must be expected to return to normal within several weeks.

Considerations on the relationship between pre- and post-operative CEA levels

However it does appear that there is a relationship between pre- and post-operative CEA levels. The thought behind the assumption of the absence of rise in normal pre-operative values, might not be entirely wrong. The likelihood CEA will rise with recurrent disease when pre-operative values were elevated as well is higher (78%, versus 50%) then with normal pre-operative levels. From this observation, it might be true that looking at relative CEA values, anticipating on an individual's 'normal value', would be a more effective manner of finding abnormalities then apprehending static cut-off values. The use of percentual rise or doubling time (DT) of serum CEA values might be effective. A strong prognostic value of this alternative has already been demonstrated,^{12,15,18–20} however, no clinical trials have been initiated up until now to study the clinical benefit. Theoretically, by analysing the rise of CEA with measurement at an interval of several weeks, both sensitivity and specificity can increase. A higher sensitivity is achieved because a rise in CEA can signal recurrent disease before crossing a static threshold, especially in patients with low baseline values. A higher specificity is expected because

incidental rises due to, e.g., self-limiting benign disease are 'filtered' by repetitive measurements. Low specificity for malignancy has been the main problem of CEA, which has also led to the apprehension of higher threshold values then actually are normal. Use of CEA rise, therewith anticipating individual differences in CEA expression, might solve this problem. An explanation for the variances in CEA expression may be the production and shedding to the circulation or intestinal lumen by different tumour types.^{21–23} Immunohistochemical staining of CEA within the cell has different cellular distribution patterns reflecting in different serum levels. This pattern of expression and successive differences in spilling to the circulation may be retained in recurrent disease.

Conclusion

The majority of patients with rectal carcinoma have normal CEA values before curative surgery and half of them will express a rise in CEA values due to recurrent disease. This means a significant number of patients will miss an opportunity on early detection of recurrent disease when CEA measurements are omitted, due a false assumption. Serial post-operative CEA testing cannot be discarded based on a normal pre-operative serum CEA.

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